Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 2-5, 7, 9, 10, 12 and 14-33 are pending in the application, with claims 2, 3, 7, 10, 12, 14, 16, 20, 21, 24, 26, 27, and 30 being the independent claims. Claims 2-5, 7, 10, 12, 14-16 and 19 are sought to be amended by the present amendment. Claims 1, 6, 8, 11 and 13 are sought to be cancelled by the present amendment without prejudice to or disclaimer of the subject matter therein. New claims 20-33 are sought to be added.

Claims 3-5, 7, and 16 have been amended to replace the phrase "P450 expressing tissues" with the phrase "the liver" or the phrase "of the liver." Claim 4 has also been amended to delete the phrase "cancers of the colon." Support for these amendments can be found in the specification, for example, at page 12, lines 15-17.

Claims 2, 12 and 14 have been amended to make them independent. Claims 3, 7, 10, and 16 have been amended to replace "by" with the more conventional term "comprising." Claim 15, which depended from cancelled composition claim 13, has been amended to depend from composition claim 14 and to replace the word "method" with the phrase "pharmaceutical composition". Claims 15 and 19 have been amended to replace "a" with "the" according to standard Markush group terminology. Finally, claim 10 has been amended to add the phrase "for the treatment of a liver disease" immediately following "cytarabine." Support for this amendment to claim 10 can be found in the specification, for example, at pages 12-14.

Support for new claims 20-33 may be found in claims 2-5, 7, 9, 10, 12 and 14-19.

These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

I. Rejections under 35 U.S.C. § 112, First Paragraph, Written Description

Claims 3-9 and 16-19 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. (Office Action, at page 2, lines 8-12.) Applicants respectfully traverse this rejection in part.

Claims 6 and 8 have been cancelled thus rendering this basis for rejection moot.

Specifically, the Examiner states:

> The specification lacks support for claims 3-9 and 16-19 as claimed. According to the specification, applicant developed a method of improving the delivery of therapeutic agents by developing phosphonate adducts of the agents. The adduct dissociates at the site of action, releasing the agent wherein applicant's invention ends. The agent alone is responsible for therapeutic activity at the point of action, and there is no evidence in the specification that applicant developed the active agent or discovered its utility.

(Office Action, at page 2, lines 13-18.)

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, for example, *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1560, 19 USPQ2d 1111, 1114

(Fed. Cir. 1991). An Applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). See also Manual of Patent Examining Procedure, § 2163, pp. 2100-164 and 2100-165, Eighth Ed. (May 2004).

Contrary to the Examiner's statement, Applicants are not required to "provide evidence that they developed the active agent [of a prodrug] or discovered its utility." (Office Action, at page 2, lines 17-18.) Instead, Applicant need only describe the claimed compounds and methods of use.

The invention of claims 3-9 and 16-19 has been described in sufficient detail that one skilled in the art can reasonably conclude that Applicants had possession of the claimed invention. The compound of Formula III and its synthesis is disclosed, for example, in Example 9. Various diseases to be treated by the methods of claims 3-9 and 16-19, are disclosed for example, at pages 12-15. Such diseases of the liver include liver cancer and hepatocellular carcinoma. At page 14 of the specification, Applicants have also described specific treatment regimens to carry out the claimed method of preventing recurrence of cancers after medical or surgical treatment using the compounds of the invention. Applicants have also described in the specification, at pages 16-18, the advantages of using the compounds of the invention, including the high liver specificity of the compounds which leads to an increase in the therapeutic index of cytarabine, and the improved pharmacodynamic half-life of the prodrugs. At pages 19-27, the specification describes various doses and formulations of the compounds, including

combinations of the prodrugs with one or more additional agents, such as oncolytic or antiviral agents. Specific oncolytic and antiviral agents are listed in the specification at page 19-22.

Applicants assert that the methods of claims 3-9 and 16-19 are sufficiently described in the specification to clearly convey the information that Applicants have invented the claimed subject matter, thus satisfying the written description requirement for these claims.

The Examiner also states that the specification lacks adequate support for claims 3 and 16-19 because these claims "are drawn to any diseases of P450 expressing tissues. The claims must recite only the specific diseases having support in the specification." (Office Action, at page 2, lines 20-22.)

To expedite prosecution and without acquiescing to the propriety of the rejection, Applicants have amended the claims to delete the phrase "P450 expressing tissues" and insert in its place the phrase "the liver" or the phrase "of the liver," so that the specific diseases, *i.e.*, diseases of the liver, are recited. Claim 4 has also been amended to delete the phrase "cancers of the colon." As claims 17-19 depend from claim 16, these claims incorporate the amendments to claim 16.

Applicants assert that the rejection of claims 3-9 and 16-19 under 35 U.S.C. § 112, first paragraph (written description), has been overcome and respectfully request that the Examiner reconsider and withdraw this rejection.

II. Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 2-3, 8, and 13-19 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. (Office Action, at page 3, lines 1-3.) Applicants respectfully traverse this rejection.

Claims 8 and 13 have been cancelled, rendering moot this basis for rejection.

Specifically, claim 2 is rejected as depending improperly from claim 1 for failure to limit the scope of claim 1. Claim 14 is rejected on a similar basis

Claims 1 and 13 have been canceled and claims 13 and 14 have been made independent, thus obviating this rejection.

Claim 15 is rejected as allegedly improperly depending from claim 13, as claim 13 is drawn to a composition while claim 14 is drawn to a method of use. (Office Action, at page 3, lines 15-16.)

To expedite prosecution and without acquiescing to the propriety of the rejection, Applicants have amended claim 15 to replace the word "method" in reference to claim 13 with the phrase "pharmaceutical composition."

Applicants believe that the rejection of claims 2-3, and 14-19 under 35 U.S.C. §112, second paragraph, has been overcome and respectfully request that the Examiner reconsider and withdraw the rejection.

III. Rejections under 35 U.S.C. § 103

Claims 1-19 are rejected under 35 U.S.C. § 103 as being allegedly unpatentable over Erion *et al.*, WIPO Publication No. WO 99/45016. (Office Action, at page 4, lines 1-2.) Applicants respectfully traverse this rejection.

Specifically, the Examiner states:

> Erion *et al.* teach a similar compound, composition and method of use for increasing therapeutic index, treating diseases of the liver, metabolic disease and cancers. M is any nucleoside, bioactive agent or drug and V is 4-pyridyl . . . . The difference between the instant invention and that of Erion et al. is that applicant is claiming [a] composition further comprising an oncolytic agent (cocktail) and M as cytarabine instead of any nucleoside, bioactive agent or drug by Erion et al. . . .The combination of compounds for a certain function where the compounds are known to have the function individually is prima facie obvious . . . . It is also obvious from routine practice of medicine of treating patients with combination therapies by using cocktail medications, administered separately or together. Therefore, the instant invention is prima facie obvious from the teaching of Erion et al. One of ordinary skill in the art would have known to use cytarabine, a known nucleoside, bioactive agent or drug, and claim a cocktail at the time the invention was made. The motivation for claiming cytarabine (a nucleoside) is from the teaching of Erion et al., that M is any nucleoside, bioactive agent or drug, and the cocktail composition is from routine practice of medicine.

(Office Action, at page 4, line 8, to page 5, line 2.)

Applicants assert that, contrary to the Examiner's statement, Erion *et al.*, in combination with the common practice of those of skill in the field of medicine, would not have rendered Applicants' invention *prima facie* obvious.

Erion *et al.*, do not teach or suggest the cytarabine (araCMP)-4-pyridyl cyclic 1,3-propanyl diester prodrugs of Formula III. See, for example, the table of exemplified compounds on pages 138-141, which does not include an example of a prodrug containing both the cytarabine and the-4-pyridyl substituents, or even an example of a prodrug containing cytosine or cytidine or its analogs. Moreover, Erion *et al.* fail to

teach or suggest the specific R and S *cis* configurations of the cytarabine-4-pyridyl prodrugs of Applicants' invention, or even discuss the specific R and S *cis* isomers of the other compounds disclosed in Erion *et al.*

The fact that a claimed species is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness. *In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994). Absent a suggestion to make and use a compound of Formula III, no *prima facie* case of obviousness has been established.

Furthermore, there is also no suggestion in Erion *et al.* to combine the claimed compounds with other oncolytic agents and use them to treat diseases of the liver.

Regarding the Examiner's statement that it is "obvious from routine practice of medicine of treating patients with combination therapies by using cocktail medications, administered separately or together" (Office Action, at page 4, lines 19-20), Applicants note that the Examiner should provide objective evidence, e.g., documentary evidence, to support this statement.

Even assuming *arguendo* that a *prima facie* case of obviousness has been established by Erion *et al.*, Applicants submit that the unexpectedly better activation of the claimed compound to give araCMP by human liver microsomes compared to a diasteriomeric isomer overcomes any basis for *prima facie* obviousness that the Examiner may assert.

Applicants respectfully direct the attention of the examiner to the Biological Examples beginning on page 69 of the specification. As reported on page 72, Compound A (which corresponds to Formula III; see page 68, lines 24-25, and Example 9) is activated at a 2.6-fold greater rate compared to Compound B. As reported on page 74,

Compound A produced significantly higher araCTP levels in the liver than Compound B at all but the 4-hour time-point.

Compound A is a 2R,4S isomer while compound B is a 2R,4R isomer (see page 68, lines 25-26). Such increased activation in the liver and the resultant increased tissue concentration is of great practical consequence. As discussed on page 1 of the specification, use of araC to treat hepatocellular carcinoma is characterized by dose limiting toxicity in organs of toxicity (e.g. bone marrow). By increasing activation in the liver, one can improve the effectiveness of araC in the liver by specifically delivering higher concentrations of araCTP to CYP3A4-expressing liver cells. This unexpected result is not taught or suggested by Erion *et al.*

Thus, Applicants assert that the Examiner has failed to establish that the compounds and methods of the present invention are *prima facie* obvious over Erion *et al.* and the common knowledge in the medical arts.

Applicants believe that the rejection of claims 1-19 under 35 U.S.C. § 103 has been overcome and respectfully request that the Examiner reconsider and withdraw the rejection.

IV. Double Patenting Rejection

Claims 1-19 are rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 34, 53-60, 95-145, and 147-172 of U.S. Patent No. 6,312,662, Erion *et al.* (Office Action, at page 5, lines 18-20.) Applicants respectfully traverse this rejection.

The Examiner states that claims 1-19 are not patentably distinct from each other and the claims of U.S. Pat. No. 6,312,662 because both sets of claims allegedly are drawn to the same subject matter. The Examiner asserts that in some of the compounds of U.S. Pat. No. 6,312,662, the variables Z, W, W' and not H at the same time and that some of these variables must be alkyl, while, in the claims of the pending application, V, Z, W, and W' are all H. However, the Examiner argues that H and alkyl are art-recognized equivalents. (Office Action, at page 5, lines 19-24.)

Applicants respectfully disagree with the Examiner and assert that Erion *et al.* provides no suggestion to make or use the compounds of pending claim 1-19, and that the compounds claimed in Erion *et al.*, U.S. Pat. 6,312,662, and those in pending claims 1-19 are patentably distinct from one another.

Applicants believe that the rejection of claims 1-19 under the judicially created doctrine of obviousness-type double patenting has been overcome and respectfully request that the Examiner reconsider and withdraw the rejection.

V. Objection to the Specification

The Examiner objects to the specification for allegedly having "numerous abbreviations, which are not common chemical nomenclature and are not defined in the specification on first occurrence in accordance with standard scientific practice." (Office Action, at page 6, lines 2-4.)

Applicants respectfully direct the Examiner's attention to pages 11 and 12 of the specification, where definitions are provided for many of the chemical abbreviations used in the specification. Moreover, Applicants note that many other technical terms are

defined throughout the specification. See, for example, the specification at page 13, lines 10-20, where several medical abbreviations are defined (e.g., OLT, TACE, AFP and CT).

Applicants believe that any abbreviations occurring in the specification that are not explicitly defined are known to those of skill in the art and, accordingly, would not require inclusion of a definition. However, Applicants invite the Examiner to give specific examples of such abbreviations in the specification that would require definitions, so that applicants may better address the Examiner's objection to the specification.

Applicants believe that the objection to the specification has been overcome and respectfully request that the Examiner reconsider and withdraw the objection.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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